

## **REMARKS**

### ***New Claims***

Claims 26-35, 42, and 61-76 are pending in the present case. In the present amendment, new claims 77-107 are added. Support for these claims is found throughout the specification.

For example:

- Claim 77 recites a 5' nuclease that is a thermostable FEN-1 nuclease. Support for the use of thermostable FEN-1 nuclease in the methods of the present invention is found in the specification, *e.g.*, at page 10, lines 23-24.
- Claim 78 recites a cleavage structure wherein the 3' portion of the second nucleic acid molecule is completely complementary to the target nucleic acid. One example of such a structure is shown in Figure 32C, where the second nucleic acid molecule is termed the "INVADER" nucleic acid. The 3' portion, shown as angled text, is completely complementary to the target nucleic acid.
- Claim 79 recites formation of a cleavage structure wherein the 3' portion of the second nucleic acid molecule partially displaces the portion of the first nucleic acid molecule that is completely complementary to said first region of said target nucleic acid. One example of such displacement by the second nucleic acid molecule is shown schematically in Figure 29, and a diagram showing sequences of the nucleic acids in such a structure is provided in Figure 41. In addition, text description of such displacement is provided, *e.g.*, in Example 11, in the paragraph at page 136, lines 17-26.
- Claims 80-107 relate to methods for detecting a target nucleic acid in a sample by cleavage with a FEN-1 nuclease. As claims directed to a method of detecting a target nucleic acid, these claims are consistent with the claims of Group I elected for prosecution in response to the Restriction Requirement mailed Dec. 17, 2002.

All of the added claims are fully supported in the specification and do not comprise new matter.

### ***Information Disclosure Statement***

Applicants note with appreciation that the Examiner has deemed applicants' argument filed 2/2/04 persuasive with respect to review of the paper copies of references provided in the parent case. In response to the Examiner's indication that the information disclosure statement filed in this case on 1/22/03 is missing from the office files, applicants provide herewith a courtesy replacement copy of that IDS.

***Claim Amendments***

Claims 26 and 73 are currently amended. Amendment of Claim 26 is discussed below. Claim 73 has been amended to recite "said first nucleic acid molecule" and "said second nucleic acid molecule." These terms are amended to more precisely parallel the antecedent for the term and not made in response to any objection or rejection by the Examiner. The amendments to the claims made herein are not intended to narrow the scope of the claims within the meaning of *Festo*<sup>1</sup> or related cases.

***Response to Claim rejections***

Claims 26-35, 42, and 61-76 are pending in the present case. The Examiner has raised the following rejections:

- I. Claims 26-35, 42, and 61-76 stand rejected under 35 USC § 112, second paragraph as being indefinite.
- II. Claims 26-29, 33, 42, 61-63, and 65-69 stand rejected as being anticipated under 35 U.S.C. § 102(b) by Lyamichev, *et al.*, Science 260:778 (1993).
- III. Claims 30, 32 and 64 stand rejected as being unpatentable under 35 U.S.C. § 103(a) over Lyamichev, *et al.*, Science 260:778 (1993), in view of Mergny, *et al.*, NAR 22(6):920 (1994).

These rejections will be addressed in the order presented above.

**I. Claims 26-35, 42, and 61-76 are not indefinite.**

The Examiner has rejected Claims 26-35, 42, and 61-76 under 35 USC § 112, second

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<sup>1</sup> *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 122 S. Ct. 1831 (2002)

paragraph as being indefinite (Office Action of June 4, 2004, page 2). First, the Examiner asserts that these claims are indefinite in that the language of Claim 26 does not clearly describe the cleavage structure formed (Office Action at page 3). For the reasons provided in the Amendment and Response filed February 2, 2004, and incorporated herein by reference, Applicants maintain that, in view of the specification and the language of the claims, one of skill in the art would clearly be able to determine the nature of a structure formed by the particular recited nucleic acids.

Nonetheless, in order to further Applicants' business interests and the prosecution of the present application in a manner consistent with Patent Business Goals, and not in acquiescence to the Examiner's arguments, and while reserving the right to prosecute the original (or similar) claims in the future, Applicants have amended Claim 26 (and thus the dependent claims) to recite that the method comprises forming a cleavage structure comprising the recited nucleic acids, wherein "at least a portion of said first nucleic acid molecule is annealed to said first region of said synthetic target nucleic acid, and wherein at least a portion of said second nucleic acid molecule is annealed to said second region of said synthetic target nucleic acid." The amendments to the claims made herein are not intended to narrow the scope of the claims within the meaning of *Festo*<sup>2</sup> or related cases. Examples of such cleavage structures in the specification include but are not limited to the diagrams shown in Figure 32C, Figure 41, Figure 60A.

The claims recite the features of the nucleic acids that form the cleavage structure, and recite the nature of the cleavage structure formed by these nucleic acids in the claimed method. As such, these claims are not indefinite and Applicants respectfully request that this rejection be removed.

## **II. Claims 26-29, 33, 42, 61-63, and 65-69 are Not Anticipated**

The Examiner alleges that Claims 26-29, 33, 42, 61-63, and 65-69 are anticipated under 35 U.S.C. § 102(b) by Lyamichev (Office Action, page 3). Applicants respectfully disagree. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d. 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.

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<sup>2</sup> *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 122 S. Ct. 1831 (2002)

1987). As explained in more detail below, Lyamichev does not set forth each and every element of Claims 26-29, 33, 42, 61-63, and 65-69.

Claims 26-29, 33, 42, 61-63, and 65-69 are drawn to a method for detecting the presence of a target nucleic acid molecule by forming a cleavage structure and cleaving the formed structure. The nucleic acids used in the cleavage structure have particular features that are recited Claim 26. These recited features relate to the structure formed.

Claim 26 recites a synthetic target nucleic acid, a first nucleic acid molecule and a second nucleic acid molecule. The synthetic target nucleic acid comprises two regions that are contiguous to each other, with the second region being downstream of the first region; “downstream” refers to the 3’ direction along a nucleic acid strand (see, *e.g.*, the specification at page 26, lines 8-11). The first nucleic acid molecule comprises a portion that is completely complementary to the first region of said target nucleic acid. The second nucleic acid molecule comprises several features: it comprises a 5’ portion that is completely complementary to the second region of the target nucleic acid, and it additionally comprises a 3’ portion. When aligned with the target nucleic acid according to the various complementary portions, the first and second nucleic acid molecules can anneal to the target such that the contiguous first and second regions of the target are both completely annealed to form contiguous duplexes. When the nucleic acids are annealed in this fashion, the 3’ portion of the second nucleic acid molecule overlaps with the duplex formed by the first nucleic acid molecule and the target nucleic acid. As described in the specification, this 3’ portion can be multiple nucleotides (see, *e.g.*, Figure 32C), or it can be a single base, or a different chemical moiety (see, *e.g.*, p78, lines 17-29).

Lyamichev fails to teach or suggest the use of a structure wherein first and second nucleic acid molecules anneal to contiguous regions of a target nucleic acid, wherein the second nucleic acid molecule further comprises a 3’ portion. Comparing the structures of Lyamichev to the structures formed in the methods of the present invention, the “substrate duplex” of Lyamichev (Figure 1A) can be compared to a duplex formed by between the target nucleic acid and the first nucleic acid molecule of the present invention. The “primer” of Lyamichev can be compared to the second nucleic acid molecule of the present invention. In the discussion of the primer, Lyamichev discusses primers that leave a gap between the 3’ end of the primer and the downstream substrate duplex and discloses primers that leave no gap (see, *e.g.*, legend for Fig. 1, page 779). However, even while teaching primers that leave no gap, such that the primer duplex

and the substrate duplex are contiguous, Lyamichev does not teach or suggest primers that additionally comprise a 3' portion that can overlap with the substrate duplex. Thus, Lyamichev does not teach or suggest the use of a primer or second nucleic acid molecule comprising a 3' portion such as is specified by the present claims. Lyamichev therefore fails to teach or suggest every element of Claims 26-29, 33, 42, 61-63, and 65-69 and does not anticipate these claims. As such, Applicants respectfully request that this rejection be removed.

### **III. Claims 30, 32, and 64 are Nonobvious**

The Examiner alleges that Claims 30, 32 and 64 are unpatentable under 35 U.S.C. § 103(a) over Lyamichev, *et al.*, Science 260:778 (1993), in view of Mergny, *et al.*, NAR 22(6):920 (1994) (Office Action, page 4). Applicants respectfully disagree. Prima facie obviousness requires 1) a suggestion or motivation in the references or the knowledge generally available to combine or modify the reference teachings; 2) the prior art must teach of a reasonable expectation of success should the suggested combination or modification take place; and 3) the prior art must teach or suggest all the claim limitations. A showing of obviousness will fail if any one of these elements is not met. The combination of Lyamichev and Mergny fails to teach or suggest all the claim limitations.

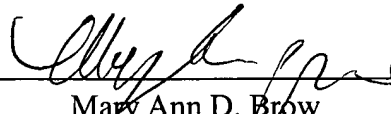
Claims 30, 32, and 64 depend from Claim 26 and incorporate all of the limitations of Claim 26. As explained above, Lyamichev does not set forth each and every element of Claim 26 (and dependent claims). In particular, Lyamichev does not teach or suggest the use of a primer or a second nucleic acid molecule comprising a 3' portion, and does not teach the use of cleavage structures such as are specified by the present claims. Mergny does not cure this deficiency.

Mergny teaches fluorescence energy transfer for probing nucleic acids by hybridization of labeled oligonucleotides. Mergny does *not* teach or suggest the use of nucleic acid cleavage structures, and does not teach or suggest the use of a primer or a second nucleic acid molecule comprising a 3' portion, such as is specified by the present claims. Thus, the combination of Lyamichev and Mergny does not teach or suggest all the claim limitations. The cited art therefore fails to establish prima facie obviousness and Applicants respectfully request that this rejection be removed.

**CONCLUSION**

For the reasons set forth above, it is respectfully submitted that all rejections should be removed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 218-6900.

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